Final Report Summaries to Board - #14 Projects
January 2016

#14-01 Design, Synthesis and Preclinical Characterization of Water Soluble Photodynamic Therapy (PDT) Therapeutics for the Treatment of Cancerous Tumors in the Tissue Transparency Window
Charles Spangler, SensoPath Technologies, Inc., Bozeman - $58,596
[Final report approved August 1, 2014]

Summary

The overall purpose of the project was to demonstrate the feasibility of creating porphyrins with meso substituents that incorporate cationic centers that render the porphyrin water soluble. The project is related to an ongoing companion project with a NIH-NCI Phase II SBIR contract researching image-guided two-photon photodynamic therapy as a more efficacious treatment of deep subcutaneous head and neck squamous cell carcinomas in humans.

In this project, SensoPath Technologies (SPT) has been able to design new model therapeutic formulations that are water soluble, and have their activation wavelengths deep in the NIR in the tissue transparency window in order to reduce the tissue absorption and scattering. Three possible therapeutic structures have been identified and model structures that incorporate pyridyl cations have been synthesized. It was also discovered that the final porphyrin structures could be simplified so that smaller subunits could be used, reducing the structure complexity and eventual therapeutic cost. Due to this advance, SPT can claim that no other porphyrins exist that can be activated at wavelengths longer and deeper in the NIR. This is a significant advance for PDT.

An additional 1-2 months of work beyond this project will be done to test new synthetic approaches to the porphyrins before testing in animals in collaboration with Massachusetts General Hospital Well Labs of Photomedicine on cancerous tumors.

SPT is an early stage pharmaceutical research and development company located in Bozeman. It proposes a significant therapeutic and technological innovation that enhances photodynamic medicine by developing a new class of light-activated Photodynamic Therapy (PDT) photo-sensitizers for the minimally invasive treatment of solid cancerous tumors in veterinary clinics that are common in companion dogs and cats.

- **Product description**

PDT is a light-based therapy that combines the use of a drug with a device for use in treating subcutaneous tumors.

- **Target market including size**

The Market Opportunity of the report discusses the numbers according to the 2013-2014 American Pet Products National Pet Owners survey. Therapeutics and diagnostics for companion animals is currently ~$33 million per year combined world revenues.

- **Estimate of sales revenues for five-year period into the future**

No sales revenue from PDT therapeutics for cancer treatment is allowed until after an NDA is approved by the FDA. (SPT's alternative treatment option would be significantly less expensive than the current standard of care for both companion animal cancer treatment and minimally invasive human cancer treatment, resulting from a relatively inexpensive laser device and a much less expensive therapeutic.)

- **Development of intellectual property**

SPT's proprietary image-driven dyads incorporate a proprietary killing photosensitive agent and non-proprietary targeting and imaging agents. The porphyrins used in all SPT dyad formulations are patent protected. The EGFR targeting peptide is a proprietary formulation designed by SPT.

- **Acquisition of investment capital**

SPT is seeking investment capital for preclinical development through Phase I clinical trials that will cost $7-8 million and last three to four years in pursuit of both a human IND and a Veterinary IND simultaneously.

Economic Impacts

The resulting therapeutics will form the basis of a Series A fund-raising effort (~ $3M). If the fund-raising efforts are successful, this will result in a doubling of the size of SPT (from four full-time employees to eight). If new investors require the human cancer PDT projects be separated from the Veterinary PDT projects, this may result in a spin-out and formation of a new company.

Revenues from the sales of cancer therapeutics will not occur until SPT obtains FDA NDA approval, estimated to be 5-6 years.

At least two new Phase II SBIR projects will be applied for based on the results of this project and using the new "Direct to Phase II" grant program that NIH has established. These proposals will probably be submitted for the December 5, 2015, NIH deadline. Each proposal will request $1M for a two-year time period. In this "Direct to Phase II" grant program, the results obtained from the one-year MBRCT project can take the place of a normal NIH SBIR Phase I, which greatly accelerates the progress of new projects that could result in commercialization.

#14-02 Clinical Evaluation of Wavefront-guided Progressive Multifocal Contact Lens
Stephen Dunn, WaveSource, Kalispell/Whitefish - $110,000
[Final Report approved August 2014]

Summary

Four key developments were required for the commercialization of wavefront-guided progressive multifocal contact lenses. Three were completed with MBRCT funding in 2010. The fourth development has now been completed under this grant.

The primary objective of this project was to validate the hypothesis that fitting WaveForm Custom Progressive Multifocal contact lenses with its unique design and manufacturing process and incorporating non symmetrical optics based on the pupil location relative to the contact lens would achieve superior visual results when compared to the currently available brands that all have optics based on the center of the lens and not the pupil of the eye. It was clear by the end of the study that the results supported the project objective well beyond the expectation of the Principal Investigator.

Patients with presbyopia represent a significant market opportunity as our population ages, and based on their visual demands are one of the hardest to satisfy. WaveForm Custom Progressive Multifocal contact lenses based on this study take a significant step forward in delivering better vision, binocularity and overall satisfaction. As the WaveForm Custom Progressive Multifocal contact lens can be prescribed and manufactured to any prescription there also exists a large patient population that cannot be served by the current "off the shelf" brands of disposable multifocal lenses. This will be the primary target for the initial commercial roll out of the WaveForm Custom Progressive Multifocal contact lens.

Commercialization

Product description

WaveForm Multifocal Progressive contact lenses that provide better vision for those currently wearing multifocal lenses as well as multifocal correction for the 20% of contact lens wearers with astigmatism that have few multifocal lens options at this time.

Target market including size

Independent Optometrists (OD) and their patients. There are an estimated 34,800 OD's in the U.S. Of these, approximately 5,400 are considered early adopters and about 100 of these are likely to adopt this new technology at the outset.

Marketing strategy - Marketing strategy will target the independent optometrists and their patients.

Production or manufacturing plan

WaveSource's cost-effective and efficient manufacturing model provides individualized Wavefront-guided progressive multifocal contact lenses utilizing a just-in-time production strategy.

Estimate of sales revenues for five-year period into the future

There are many variables that make sales and earnings projections difficult. The financing model illustrated in the report was incorporated in the Company's 2012 business plan and requires a funding round to raise $2,000,000. The company hasn't yet implemented the funding round but states the projections are obtainable once the funding is in place.

Economic Impacts
The study validated the vision benefits of producing multifocal progressive contact lenses with asymmetrical optics centered over the pupil. Unexpectedly the study provided several other potential value-added possibilities for the Company. The work performed by the Flathead Valley Community College to fully automate the WaveForm contact lens manufacturing and lens design program has provided a powerful utility that the Company will be able to license to other contact lens manufacturers and has already licensed to labs in the USA, Italy and Korea.

#14-08 Compact Compressive Laser Ranging System
Zeb Barber, Montana State University, Bozeman - $139,144
[Final Report approved April 2015]

Summary
The research focused mostly on Objective (1), which provides the technology feasibility, i.e. demonstrating the high speed digital signal generation and compressive sensing range profile recovery used in the CLR technique using only the resources provided by a Field Programmable Gate Array (FPGA). The FPGA development was performed by a Master's student in Electrical Engineering and his Master's thesis is based on this project. The project resulted in the ability to address and demonstrate that all functions of the CLR technique can be accomplished with a practical, compact, and cost-effective system. However, full integration of the system into a compact form factor was not achieved.

Achievements of Objective (2) were not met due to their dependency on achieving Objective (1), which initially met slow progress.

Achievements of Objective (3) largely met and/or exceeded expectations. Successful demonstration of the coherent CLR technique points to one way to achieve a full 3D imager based wholly on compressive sensing techniques.

Overall, the project was successful in that it provides a path to making a compact and relatively inexpensive CLR system. The ideal application space that would take full advantage of benefits provided by a CLR based ranging or 3D imaging system has not yet been determined. Thus, the ideal first market has not been determined either.

Commercialization
The ideal application space that would take full advantage of benefits provided by a LR based ranging or 3D imaging system has not yet been determined. Therefore, the ideal first market has not been determined either, making a Commercialization Plan premature at this time.

#14-15 New Technology for Determining the Abundance and Ratios of Biologically Important Metabolites in Live Cells
Mensur Dlakic, Montana State University, Bozeman - $117,297
[Final Report approved June 2015]

Summary

The objective of the project was to develop novel technology to determine the abundances and ratios of biologically important metabolites in live cells. The technology would be a revolutionary game changer for understanding how cells respond to their environments and to the nutrients they receive. The collaboration between three labs at MSU created three different dyes, and two more are under development. Additional basic research needs to be done before the technology is commercially viable. However, the project holds great promise for both scientific application and commercial development. It is envisioned that after the dyes are completed and tested in cells, the technology will add value to Montana's tech industry, i.e. optics and biotechnology. The primary avenues for commercial are development of novel, conditionally fluorescent dyes for sale to researchers, and development of instrumentation as a quick diagnostic tool. Both applications will be pursued with Montana-based collaborators in the near future.

Commercialization

The project is not at a point where it can be commercially viable as more basic research needs to be done. Additional funds are being sought to continue the work. A NIH grant was submitted in October 2014 for $396,000 but did not receive funding. It will be resubmitted in 2015. It is felt that the project has great potential for both scientific application and commercial development. The main strength of the project is its innovation in three technology aspects, the first two of which have commercial potential:

1) Development of novel, conditionally fluorescent dyes, which are made using in-house developed synthesis, and will be sold to interested researchers.

2) Ability to quickly and simultaneously measure changes in concentration of many small molecules in cells, thus providing a quick diagnostic tool. This work will continue in collaboration with Resonon to develop instrumentation to perform these experiments.

3) The technology will be applied to several new research directions underway at MSU that will be benefitted by this project.

#14-16 Sustainable Coal Bed Methane (CBM) and Biofuel Production from Algae Grown in CBM Producer Water
Matthew Fields, Montana State University, Bozeman - $140,866
[Final Report approved January 2016]

Summary

The goal of this project was to conduct research on the enhancement of coal-dependent methanogenesis using a mixture of algal extracts and other nutrients. In addition, it was proposed to grow algae in CBM (coal-bed methane) production water that would accumulate lipids as well as provide nutrient amendment for the stimulation of coal-dependent methanogenesis, and to develop a flow-through column reactor for the growth of methanogenic cultures.

The project demonstrated that algal extracts stimulated coal-dependent methanogenesis in a similar amount compared to yeast extract. An alga was isolated from CBM production water and demonstrated that it could grow in CBM production water once particular nutrients were added. The alga was shown to also accumulate lipids when grown in amended CBM production water. A prototype reactor was constructed and improved to allow the growth of methanogens during flow-through operation. Ultimately, large-scale algal production in CBM ponds could substantially increase CO2 uptake from the atmosphere, thereby decreasing the carbon footprint of conventional CBM operations. Re-injection of amended CBM water reduces the quantity of this non-potable water that needs to be treated and/or discharged. The achieved results have implications for the development of sustainable water and resource recycle for the energy sector in Montana and the region.

Commercialization
Based on results obtained from laboratory work, the goal of Objective 3 was to design a field pilot study. A preliminary field-pilot-scale system was designed. The field study will show the feasibility of the technology at an actual CBM site in partnership with the US Geological Survey. The narrative describes the pilot project tasks, equipment costs, and operating costs. It is estimated that the pilot-scale demonstration of the technology can be implemented in the field for about $360,000.

Other
Additional support has been awarded to Montana State University in the form of follow-on funding in collaboration with the University of Arizona or MET, in the combined amount of $1,477,113.

A manuscript describing the project results was presented in June 2015 at the national meeting for the American Society of Microbiology and has been submitted for publication.

#14-29 In-Vivo Testing of a Novel Compound, WT13-12, as a Treatment for Infected Wounds
Thomas Rau, Wintermute Biomedical, Missoula - $42,786
[Final Report approved May 2014]

Summary
This project was funded to study the anti-bacterial effects of WT13-12 in a wound model of infection. Results of the first study group involving methicillin-resistant Staphylococcus aureus (MRSA) were deemed “highly successful”.

Commercialization
Based on the results of the studies, commercialization potential of WT13-12 appears to be significant. An SBIR grant has been written and will be submitted to complete the pre-clinical studies and file the investigational new drug with the Food and Drug Administration. Phase II goals will include filing with the FDA for an investigational new drug (IND). A contract research organization (CRO) will be hired to help prepare

and file the IND. Options in case the SBIR Phase I is not awarded are included in this section of the final report. For the animal veterinary aspect of product development, negotiations are under way with a local veterinarian who will conduct a pilot study in domestic animals that have topical fungal infections. The process for gaining FDA approval for animal use as a topical agent is also under way.

Economic Impacts

The grant was a small pilot application that fulfilled a critical need: validation of *in-vitro* findings in an animal model. This type of validation cannot be overstated; further commercial development is not possible until proof-of-concept studies are completed. This grant provided the necessary studies and scientific justification to move into a larger validation study and then file the investigational new drug application with the FDA. The University of Montana also received funding in terms of cage charges and animal billing. The grant allowed Wintermute to develop a product that will eventually move into clinical treatment and commercialization. Wintermute Biomedical LLC is also developing two other products concurrently, and it is hoped that the development of these products will create a small niche market in Montana that will expand Wintermute and its employee base.

#14-30 Enhancement of Applied/Translational Research in Biomedicine
Richard Bridges – University of Montana - $149,078
[Final Report approved December 2015

Summary

The overall goal of the NIH-funded COBRE award was to establish *CSFN* for the purposes of increasing critical mass of researchers and providing the needed infrastructure to increase the competitiveness of biomedical research efforts in Montana. In turn, the overall goal of the MBRCT award was to supplement this effort in a manner that would positively impact economic development in Montana within the area of applied biomedical research. In addition to several academic units within the University of Montana, this project also included working with clinical entities, such as the Montana Neuroscience Institute and the Neural Injury Center, as well as with emerging biotech companies in Montana.

Significant progress has been made to enhance applied biomedical research efforts in the state, specifically in the areas of: increasing critical mass of scientists engaged in applied research (Aim I), supporting shared instrumentation (Aim II), training students (Aim III), enhanced training and opportunities for tech transfer (Aim IV), and increasing opportunities for private sector collaboration and IP commercialization (e.g., SBIR awards, university-private sector collaborations) (Aim V). This award overlaps with that of MBRCT award #15-19 (currently in no-cost extension) and shares some of the same benchmarks and accomplishments.

Significant accomplishments of this award include:

- Over **$1.3M** in total new funding was awarded to CSFN investigators and a total of more than **$39.2M** in grants were submitted by CSFN researchers, many of which are still pending a funding decision.

• CSFN investigators continue to increase the number of ongoing collaborative ties established with emerging Biotech companies in Montana, especially with those in the immediate vicinity of UM and MSU, as well as national companies (TranSynaptic, Sinapis, Revalesio, DermaXon, Rio Pharm., ADVR, Promentis Pharm).

• **Eight** new pieces of intellectual property were advanced to the point of filing either provisional or full patents. These pieces of IP will play an integral role in the ability of CSFN faculty to establish partnerships with existing companies and/or the creations on new biotech spin-offs.

• **Twenty-nine** students participated in the Summer Undergraduate Research Fellowship program, receiving hands-on experience in biomedical and translational research.

Collectively, this project is intended to have a long-term positive impact on Montana's economy by first increasing jobs through the acquisition of federal research grants and contracts, secondly by enhancing collaborations with private sector companies, and lastly by developing (and protecting) intellectual property that can be commercialized through existing or new companies. It is within this last mechanism that there is the greatest potential for the direct commercialization of technology. During the past award period, continued progress was made in each of these areas.

Commercialization

The most effective strategy for enhancing the capability of university-based research to positively impact regional economies is to: (1) increase the critical mass of scientists and projects directly associated with applied research; and (2) enhance the opportunities to develop appropriate projects via collaborations with biomed/biotech companies. Thus, the project has been more focused on enhancing discovery, capturing it as intellectual property, and transferring it to the private sector than on commercialization of a single technology or product. This has been the appropriate strategy for long-term growth and impact, as well as the one best suited for the role that the University should play in economic development. The most successful projects have relied on the academic environment of the CSFN to help develop the product/technology and on the collaborating private sector company to commercialize it. The development of a commercialization plan only occurs after collaboration has been initiated and then, the commercialization plan is developed by the corporate side of that collaboration. The strength of this strategy is exemplified by the fact that a number of recent seed projects have developed to the point where they have spun off new companies or partnered with existing companies to apply for and/or attract independent SBIR and MBRCT support, that is in part reliant upon the companies' competitive commercialization plan (as demonstrated by Sinapis, Revalesio, DermaXon, Rio Pharma., ADVR, Promentis Pharm). Thus, commercialization plans are developed for each of the different projects at the appropriate time as dictated primarily by funding needs, such as SBIR grants or investments proposals to angel investors or venture capital groups.

Economic Impacts

The economic impact of the project is long-term and focused on capturing IP developed by CSFN investigators and then effectively transferring it to the private sector via collaboration and tech-transfer. That being said, each of the Specific Aims inherently has an economic impact.

Aim I Enhance the critical mass of competitive neuroscientists and projects within Montana that are actively engaged in applied research related the development of novel diagnostics, pharmaceutical reagents, devices, processes, and/or therapeutic agents related to the treatment of brain injury and disease.
The $1.3 million in extramural grants garnered by CSFN investigators during the award period has had a significant impact on Montana's economy. Further, it is estimated that the "Business Activity Multiplier" for NIH awards in Montana has been determined to be between 1.9 and 3, translating into a minimal total impact of more than $2.5 million. As about 60% of grant funding is typically directed toward salary for staff, students and faculty, this funding has helped create and/or maintain numerous jobs. This is a particularly important consequence of research funding given the current status of the economy and unemployment in Montana.

Aim II Enhance the ability of applied and basic researchers on and off campus to access needed high-cost, high-tech shared instrumentation facilities.
Equipment in the instrumentation cores has been used by both university and private sector researchers. In collaboration with emerging Montana companies, this access has saved the companies the cost of acquiring such instrumentation, which would often be unobtainable. Further, access to this equipment is often an important factor in determining the competitiveness of grants submitted by CSFN investigators. This effort has also been markedly advanced by the development and use of the Translational Incubator lab.

Aim III Enhance "hands-on" technical training for undergraduate and graduate students in applied and basic research.
Although admittedly long-term, the student training opportunities supported by this project contribute to developing a stronger bio-tech work force. Collaborations with private sector companies have also added to new job creation for students involved in the projects.

Aim IV Enhance training and opportunities for technology transfer and commercialization based upon the recognition, development, and protection of intellectual property emerging from the laboratories of the neuroscientists within the CSFN.

Aim V Utilize the results of Aims I-IV to develop and/or strengthen ties with emerging biomed/biotech companies in Montana with the goal of commercialization.
Enhancing university/private sector collaborations as a way to increase economic development has been a major goal of this project. The two most important outcomes of this project have been a marked increase in the generation of intellectual property and the

creation and/or continued collaboration with both MT-based and national biotech companies (e.g., TranSynaptic, Sinapis, Revalesio, DermaXon, Rio Pharma., ADVR, Promentis Pharm.). These efforts and companies represent a critical step in the development of the bio-tech sector in Montana.

Overall, the design and implementation of this project represents one of the best ways in which university-based research can be leveraged and directed toward economic development in Montana.

#14-34 Investigating the Therapeutic Potential of BH31-1, a Small Molecule Inhibitor of Fungal Morphogenesis
Kurt Toenjes - MSU Billings - $99,400
[Final Report approved February 2015]

Summary
The fungal pathogen *Candida albicans* causes both superficial and life-threatening systemic infections, and is the leading cause of fungal disease in immunocompromised individuals. Due to its ability to block filamentous growth in *C. albicans*, the small molecule BH3I-1 has the potential to form the basis for a novel approach to controlling fungal infections in humans. However, its potential as an antifungal prophylactic or therapeutic was unknown at the time the project was proposed. Three specific aims to improve and assess the therapeutic potential of BH3I-1 in treating *C. albicans* infections were proposed.

Commercialization
The successful reduction of the fungal burden in mouse kidney suggests that BH3I-1, and possibly its derivatives, has potential as an anti-fungal therapy and moves the effort significantly closer to commercialization. The treatment protocol still needs to be refined and derivatives identified that will clear the infection within the time period of the treatment protocol. Both of these goals are ongoing.

Economic Impacts
Six undergraduates were training during the course of this project. One of the students earned the prestigious Goldwater scholarship (a nationally competitive undergraduate research scholarship). Also, a technician completed her Master's degree at John's Hopkins University. Two students have been accepted into Medical School (Fall 2015 matriculation) and the others continue to work in the laboratory. Two university faculty and one research faculty member also earned salary for their work during the summer of 2014.

#14-35 Evaluation of a Novel Renewable Bio-fiber Based Filter to Remove Mercury from Flue Gas
Kumar Ganesan, Montana Tech, Butte - $90,000
[Final Report approved August 2015]

Summary

The main goal of this project was to develop a marketable bio-fiber based metallic nanoparticle filter to remove mercury from air stream. The research focused on evaluating a novel "bio-fiber" as the substrate in the filtration system. This is a new innovation that advances the state-of-art in its field. The results of the research conducted sowed the bio-fiber MNP filters showed over 90% efficiency in capturing mercury from flue gas. The fiber filter can be regenerated if needed to recover the captured mercury. The cost of the system is estimated to be in the range of $1 million compared to the cost of carbon injection costing about $15 million. The application for the filter in smaller operations is positive and this is the avenue being explored for marketing the filters. The PI is invited to speak at a clean coal conference in Xian China in September 2015, which will present opportunities for exploring the Chinese market. In summary, the bio-fiber based metallic nanoparticle (MNP) filter is a newgeneration of filters that will help reduce mercury from entering the environment from power plants and from other air emission sources.

Commercialization

The feasibility of commercializing the technology by manufacturing in Montana vs. licensing the technology to an out-of-stage group was evaluated. It was estimated that a total of $3.08 billion worth of market is expected in the US alone. This does not involve new plants constructed to meet rising US and Chinese electricity demand. All new facilities must have mercury control systems in place. Therefore, the market outlook for effective and proven mercury control systems appears bright.

Because Montana has large coal deposits, if successful, the bio-fiber MNP mercury filters will help the Montana economy.

Economic Impacts

New businesses created or expanded

The PI has established a private company, Energy and Environmental Research and Technology, LLC, 400 West Park Street, Butte, to commercialize the technology.

#14-40 Production of Aviation Fuels from *Camelina sativa* Oil through Heterogeneous Catalysis

Md Joynal Abedin, MSU Northern – Havre - $30,607

[Final Report approved February 2015]

Summary

To address the need to reduce the environmental impact of air transportation and increase U.S. energy independence, MSU-Northern's Bio-energy Center has been pursuing bio-energy related research with a focus on Montana-sourced biomass. The Center has been working on developing bio-jet fuel from Camelina as a viable alternative to traditional petro-jet fuel, in particular a novel heterogeneous Grubbs catalyst and robust chemical conversion methods to convert biomass into aviation fuel. As a main focus of the research project, the group pursued two separate pathways for synthesizing the heterogeneous novel catalyst with two specific properties: robust catalytic activity and recyclability of the catalyst. Two different pathways to achieve the synthetic goal were pursued. The research findings and future research on conversion technology are

expected to catalyze the development of Camelina sativa as an energy crop in Montana. The results of the research may also provide the tools and knowledge necessary to commercialize and put Montana grown Camelina at the forefront of American bio-energy production. As a result of this research Camelina derived biofuel will contribute in the reduction of GHG emissions associated with transportation fuels.

Commercialization

The project supported two related, but distinct, products that can be commercialized separately, the heterogeneous Grubbs catalyst and Camelina biomass next-generation fuels. Although the Grubbs catalyst is an important component for economic viability of Camelina advanced fuels, it also has applications in other industries and has the potential to be commercialized separately from the fuel. The Grubbs catalyst is very expensive, and proprietary issues will play an important role in commercial application of the catalyst. The commercial impact of this catalyst is huge. This catalyst will not only be applied for metathesis of Camelina oil for jet fuel synthesis but has potential application in pharmaceutical products and other chemical industries. Pharmaceutical and chemical industries are currently using homogenous Grubbs catalysts that are in need for a robust heterogeneous Grubbs catalyst. Heterogeneous catalysts will increase the recyclability of the catalyst and reduce the purification cost hence dramatically reduce the product cost.

Economic Impacts

Results of the project will be submitted for US patent after fully characterizing the catalyst**.**